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Tiotropium and its efficacy in the treatment of COPD

Tiotropium w terapii POChP

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Abstract

Exacerbations of chronic obstructive pulmonary disease (COPD) have a negative effect on the clinical course and outcome of the disease thus causing considerable social and economic burden. As the natural course of the disease may vary, the treatment should take into account an individual approach to a patient. The appropriate treatment makes it possible to control the symptoms, improves effort tolerance and decreases the risk of exacerbations and death. Tiotropium is a muscarinic receptor antagonist, which is taken once daily, in maintenance therapy, in every stage of the disease progress. The efficacy of tiotropium in regards to exacerbations of chronic obstructive pulmonary disease has been evaluated in many clinical trials against placebo and several different active comparators. This review presents the results of those studies with the main goal to evaluate the efficacy of treatment with tiotropium in terms of prevention and course of exacerbations.

Key words: tiotropium, COPD, exacerbations

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Streszczenie

Zaostrzenia przewlekłej obturacyjnej choroby płuc (POChP) mają istotny wpływ na przebieg kliniczny oraz stopień kontroli astmy, stanowiąc istotne obciążenie społeczne i ekonomiczne. Historia naturalna i przebieg choroby mogą się różnić między pacjentami, dlatego leczenie powinno uwzględniać indywidualizację terapii. Odpowiednie leczenie pozwala na kontrolowanie objawów, poprawia tolerancję wysiłku i zmniejsza ryzyko zaostrzeń i śmierci. Tiotropium jest antagonistą receptora muskarynowego, podawanym raz na dobę, w terapii podtrzymującej na praktycznie każdym etapie rozwoju choroby. Skuteczność tiotropium w odniesieniu do zaostrzenia przewlekłej obturacyjnej choroby płuc oceniano w wielu badaniach klinicznych w porównaniu z placebo i innymi lekami. W pracy przedstawiono wyniki tych badań, ze szczególnym uwzględnieniem oceny skuteczności tiotropium w zakresie zapobiegania zaostrzeniom.

Słowa kluczowe: tiotropium, POChP, zaostrzenia

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Epidemiology

Chronic Obstructive Pulmonary Disease (COPD) is one of the major global causes of morbidity and mortality. The disease causes over 3 million deaths globally, which accounts for 6% of all deaths [1]. Approximately 5–10% of adult population aged above 40 years in Europe is suffering from COPD. Mortality caused by COPD in the population of Europe is estimated at 18/100,000 people (age-standardised coefficient) [2]. The results of a multi-center, international epidemiological study, called BOLD (Burden of Obstructive Lung Disease), which assessed in-

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cidence and factors of the diseases progress, have shown the incidence to vary from one country to another and to be higher in males than in females [3]. The incidence of COPD has been found to increase with age and the number of cigarettes smoked (the number of pack-years) [4, 5]. The incidence of COPD in the southern region of Poland (Małopolska), as estimated in the study, was 10.9% (13.3% of males and 8.6% of females) [6].

COPD is a disease with multifactorial aetiology and varied course, and it requires an individual approach to each patient. A secondary analysis of the findings of the ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) conducted with currently applied categorisation of patients into groups A, B, C, D (as per 2011 GOLD guidelines), revealed significant differences between groups of patients across a wide range of the parameters under analysis [7]. It was observed that patients who were initially classified into groups A or D usually remained in those groups after 3 years of observation, unlike the patients initially assigned to groups B or C. The risk of exacerbations was found to increase with the disease category from A to D, whereas the risk of hospitalisation and mortality was the lowest in group A, and the highest in group D, with medium and equal levels in groups B and C, although group B by definition includes patients with mild or moderate obstruction and a lower risk of exacerbations. Moreover, the highest percentage of patients with co-morbidities and patients with chronic systemic inflammation was found in group B. These observations can have important clinical implications as they suggest that patients classified into group B should be examined particularly actively for co-morbidities because there may be other causes of hospitalisation and mortality in this group of patients other, than only severe exacerbations of COPD.

The choice of therapy depends on the category into which a patient has been classified (A, B, C or D according to the latest GOLD guidelines) [8]. The appropriately selected treatment makes it possible to control the symptoms, improves effort tolerance and decreases the risk of exacerbations and death.

Exacerbations of COPD

According to GOLD, "an exacerbation of COPD is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication" [8].

Exacerbations of COPD are characterised by sudden increase in breathlessness, cough and/or increase in the volume of sputum. Severe exacerbations involve worsening of gas exchange, hypoxemia, which may be accompanied by hypercapnia. It is estimated that as many as 50% of all exacerbations are not reported by patients and remain untreated. Although their course may be mild, unreported exacerbations are not without an effect on the health status [9, 10]. Exacerbations accelerate the loss of pulmonary function, which is typical of COPD and which results in worse effort tolerance and a decrease in patients' daily activity. Episodes of severe exacerbations leading to hospitalizations are found in all patients, regardless of the disease stage and they have a negative impact on prognosis – as they contribute to increased mortality. Patients at high risk of exacerbations leading to hospitalisation are those with a history of similar events as well as patients with worsened pulmonary function, deteriorated health status, leukocytosis or symptoms of pulmonary oedema revealed radiographically [11]. Frequent exacerbations entail large economic and social costs which are generated by more frequent outpatient visits, hospitalisations, increased consumption of drugs, sick leaves and disability benefits [8, 12]. Prevention, active and early diagnosis and early, correct treatment of exacerbations is of key importance in efforts to reduce the costs associated with COPD.

The observations made as part of the ECLIPSE study showed that the frequency of exacerbations increases with the disease progression, although a group of particularly susceptible patients can be identified, defined as those who suffer from exacerbation episodes relatively often (at least twice a year) [13]. This attracted attention to the existence of a phenotype which involves frequent exacerbations, regardless of the degree of airway obstruction. The phenotype with frequent exacerbations was stable during a three-year observation (Table 1).

Causes of exacerbations

Impairment of the topical defensive mechanisms within the respiratory system makes patients with COPD more susceptible to infections. Viral infections of upper airways are the cause of 30–60% of all the exacerbations [15]. Usually, viral agents include rhinoviruses (20–25%), whereas RSV, influenza viruses, para-influenza viruses, adenoviruses and coronaviruses cause 5–10% of all COPD exacerbations. Bacteria

Table 1. Characteristics of the phenotype of COPD with frequent exacerbations according to [14]

Tabela 1. Charakterystyka fenotypu pacjentów z POChP i częstymi zaostrzeniami choroby [14]

Faster deterioration in FEV_1
Increased risk of hospitalisation and mortality
Exacerbated inflammatory condition (higher concentration of IL-6, fibrinogen, CRP)
Higher susceptibility to viral infections
A larger number of bacteria that colonise lower respiratory tract
Lower quality of life (as measured by SGRQ*)
An increased risk of cardiovascular diseases

*St George's Respiratory Questionnaire

cause 50% of all the exacerbations. Majority of exacerbations are caused by: *Haemophilus influenzae* (20–30%) *Streptococcus pneumoniae* (10–15%) and *Moraxella catarrhalis* (10–15%). Bacterial aetiology of exacerbations may vary and depend on the disease advancement, frequency of exacerbations and the type of antibiotic therapy applied. *Pseudomonas aeruginosa* are frequently isolated in patients with severe exacerbations, in an advanced stage of the disease (5–10%). There has been a low correlation shown to exist between acquisition of a new strain of *H. influenzae, S. pneumoniae* and *M. catarrhalis* and exacerbation of COPD [15]. Compared to exacerbations of COPD with bacterial aetiology, exacerbations initiated by viruses and exacerbations with mixed (viral and bacterial) aetiology have a more severe course, they last longer and the risk of hospitalisation is higher [9]. 15–20% of exacerbations are caused by non-infection-related factors, including air pollution and tobacco smoking. Exacerbation may also result from incorrect drug inhalation or from giving up maintenance therapy.

Prevention of exacerbations

All measures which lead to a decrease in the incidence of exacerbations are beneficial both from the perspective of a patient as they contribute to the improvement of the quality of life and slowing down the disease progression, and from the perspective of the healthcare system as they reduce the cost of COPD treatment. The recommended measures include giving up smoking, vaccinations against influenza and pneumococci (especially in patients aged > 65 years), respiratory rehabilitation and daily exercise [8].

Chronic use of antibiotics is not recommended in the prevention of COPD exacerbations due to insufficient clinical evidence to confirm the efficacy and safety of such measure [8]. Some analyses have suggested benefits to be gained from using antibiotics in COPD patients, especially at an advanced stage of the disease. A meta-analysis of 6 clinical trials conducted with 1677 patients with severe and very severe COPD, most of them with a history of at least one episode of exacerbation, has revealed the risk of exacerbations in patients who receive macrolides being lower by 37.3% than in patients who received placebo [16]. The risk of hospitalisation has also been shown to be lower by 21% in patients who received an antibiotic. On the other hand some issues of potential safety of chronic antibiotic use and risk of increase of antibiotic resistance at the population level are raised. Further studies are needed to clarify the potential role of antibiotics in the prevention of COPD exacerbations.

The role of tiotropium in therapy of chronic obstructive pulmonary disease — a review of clinical trials

Tiotropium bromide is a long acting and relatively selective muscarinic antagonist (LAMA). It is the slowest to dissociate from the M3 receptor, which results in its considerable and prolonged bronchodilating effect. Bronchodilation is a result of local, rather than systemic, effect. The onset of the drug action takes place after approx. 30 minutes and its action is maintained for over 24 hours.

Tiotropium is used in maintenance therapy in every category of COPD advancement; it is a second choice therapy in category A. Tiotropium can be taken once daily at the dose of 18 μg from a dry powder inhaler (Hendihaler) or at the dose of 5 μg (two actuation 2.5 μg each) from a soft mist inhaler (Respimat). Higher deposition rate (39% vs 11% Respimat vs MDI) of the drug in lungs is achieved when administered with a Respimat inhaler which makes it possible to use a smaller dose. The TIOSPIR (Tiotropium Safety and Performance in Respimat) study conducted with 17,135 COPD patients showed that the safety profile and efficacy of two available formulations of tiotropium are comparable [17]. The risk of death from any causes, the risk of cardiovascular death, the risk of severe cardiovascular incidents and adverse reactions as well as the risk of COPD exacerbations, including those requiring hospitalisation, were similar. The efficacy and safety of tiotropium have been evaluated in many clinical trials against placebo and several different active comparators (Table 2, Fig. 1).

Table 2. Summary of results of analyses comparing the effect of tiotropium vs a comparator on COPD exacerbations

Tabela 2. Podsumowanie badań analizujacych wpływ tiotropium w porównaniu z innymi lekami badanymi na zaostrzenia POChP

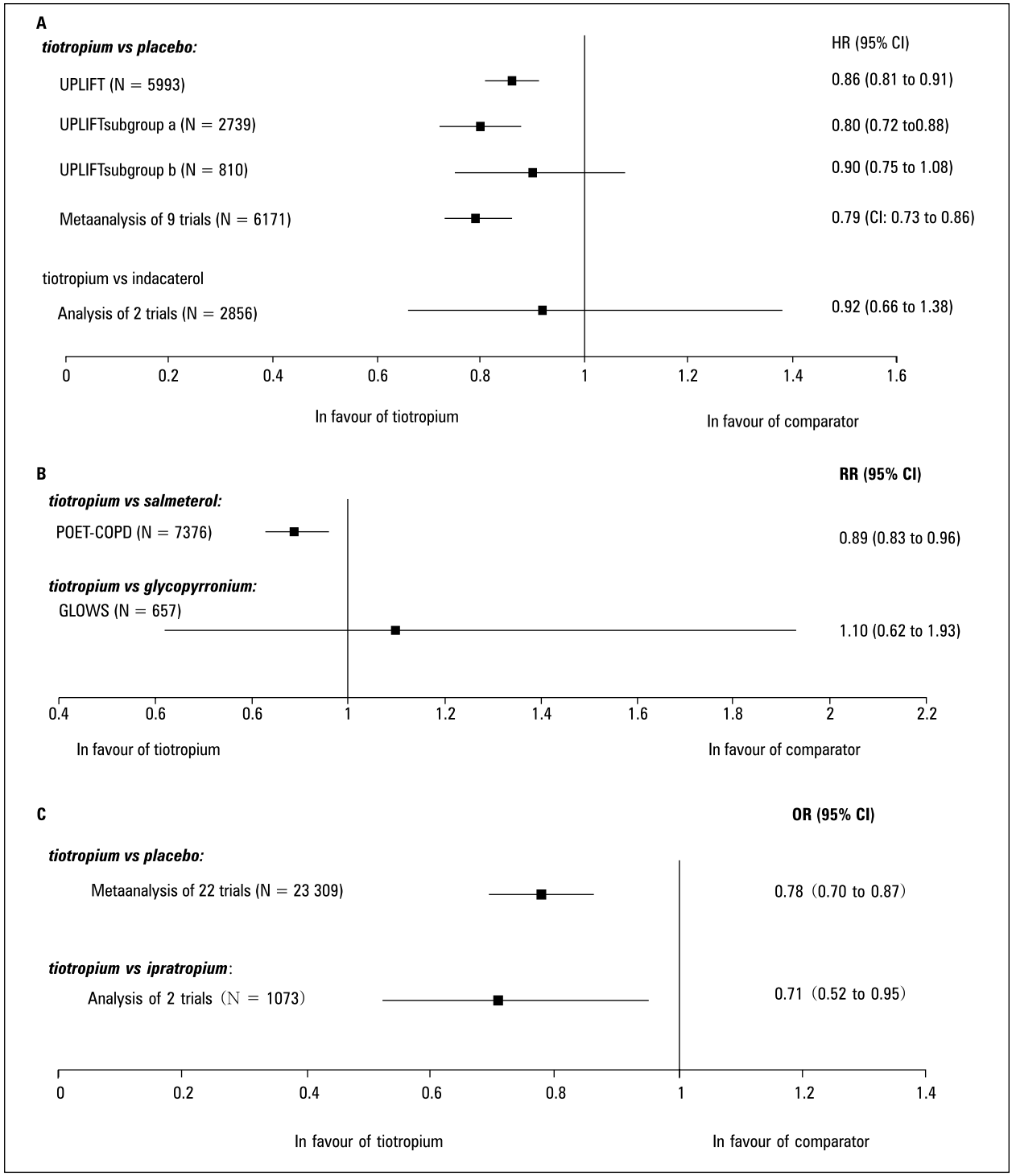
Analysis	Study (treatment duration/ endpoint[a])	N (n in the tiotropium group)	Incidence of exacerbations (reduction in risk)	Time to first exacerbation (reduction in risk)	Other exacerbation indexes
Tiotropium vs placebo	UPLIFT (48 months/Y) [18]	5993 (2987)	HR 0.86 (95% CI: 0.81 to 0.91)	HR 0.86 (95% CI: 0.81 to 0.91)	Hospitalised exacerbations HR 0.94 (0.82 to 1.07) time to first exacerbation — HR 0.86 (95% CI: 0.78 to 0.95) duration of exacerbations – HR 0.89 (0.83 to 0.95) duration of hospitalisation due to exacerbations — HR 1.01 (0.87 to 1.18)
	UPLIFT — subgroup[b] (48 months/Y) [19]	2739 (1384)	HR 0.80 (95% CI: 0.72 to 0.88)	HR 0.82 (95% CI: 0.75 to 0.90)	Hospitalised exacerbations — HR 0.80 (95% CI: 0.63 to 1.03) time to first hospitalised exacerbation — HR 0.74 (95% CI: 0.62 to 0.88)
	UPLIFT — subgroup[b] (48 months/Y) [20]	810 (403)	HR 0.90 (95% CI: 0.75 to 1.08)	nd	nd
	Meta-analysis of 9 studies (24 to 48 weeks/Y) [21]	6171 (3309)	HR 0.79 (95% CI: 0.73 to 0.86)	nd	hospitalised exacerbations — HR 0.79 (95% CI: 0.65 to 0.96)
	Meta-analysis of 22 studies† 3 to 48 months/Y) [22]	23,309 (12,697)	OR 0.78 (95% CI: 0.70 to 0.87)	nd	hospitalisation caused by exacerbations – RR 0.85 (95% CI: 0.71–1.00)
Tiotropium vs salmeterol	POET-COPT (12 months/Y) [23]	7376 (3707)	RR 0.89 (95% CI: 0.83 to 0.96)	HR 0.83 (95% CI: 0.77 to 0.90)	Time to first severe exacerbation — HR 0.72 (95% CI: 0.61 to 0.85) moderate exacerbation — RR 0.93 (95% CI: 0.86 to 1.00) severe exacerbation — RR 0.73 (95% CI: 0.66 to 0.82) exacerbation treated with glucocorticosteroids administered systemically — RR 0.82 (95% CI: 0.76 to 0.90) exacerbations treated with antibiotics – RR 0.90 (95% CI: 0.84 to 0.97) exacerbation treated with glucocorticosteroids administered systemically and antibiotics – RR 0.80 (95% CI: 0.73 to 0.88)
Tiotropium vs ipratriopium	review of 2 studies (12 weeks and 12 months/N) [24]	1073 (716)	OR 0.71 (95% CI: 0.52 to 0.95)	nd	hospitalised exacerbations – OR 0.56 (95% CI: 0.31 to 0.99) *one study data*
Tiotropium vs glycopyrronium	GLOW5 III phase clinical trial [26] (12 weeks/Y)	657 (330)	RR 1.10 (95% CI: 0.62 to 1.93)	HR 1.33 (95% CI: 0.76 to 2.33)	hospitalised exacerbations – OR 0.79 (95% CI: 0.21 to 2.94) exacerbation treated with glucocorticosteroids administered systemically – OR 1.06 (95% CI: 0.55 to 2.04) exacerbations treated with antibiotics – OR 1.48 (95% CI: 0.77 to 2.85)
Tiotropium vs indacaterol	pooled analysis of 2 studies (12 and 26 weeks/N) [27]	2856 (1221)	HR 0.92 (95% CI: 0.66 to 1.38)	nd	nd

HR — hazard ratio, CI — confidence interval, OR — odds ratio; RR — relative risk, nd — no data

[a]Y/N — Evaluation of exacerbations as a study endpoint YES/NO

[b]patients with moderate COPD (stage II according to GOLD)

[c]a subgroup of patients so far untreated/in whom tiotropium was used as the first maintenance therapy



[a]patients with COPD at stage II according to GOLD
[b]patients so far untreated/in whom tiotropium was used as the first maintenance therapy

Figure 1. The effect of tiotropium vs comparator on the incidence of COPD exacerbations – the effect expressed as: hazard ratio (HR; **A**); relative risk (RR; **B**) or odds ratio (OR; **C**). Own compilation based on [18–24, 26, 27]

Rycina 1. Wpływ tiotropium w porównaniu z innymi lekami badanymi na częstość występowania zaostrzeń POChP przedstawiony jako współczynnik ryzyka (HR; **A**), ryzyko względne (RR; **B**) i iloraz szans (OR; **C**). Opracowanie własne na podstawie [18–24, 26, 27]

Tiotropium vs placebo

The double-blind, randomised study UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) evaluated the benefits of using tiotropium for 4 years at the dose of 18 μg compared to placebo [18]. There were 5993 patients taking part in the study (including 2987 in the tiotropium group) aged at least 40 years, with moderate to severe COPD, with a history of smoking of at least 10 pack-years. The patients could receive COPD drugs according to GOLD guidelines except for other anticholinergic inhalation drugs. Evaluation of progression of lung function impairment was the primary endpoint. Other evaluated parameters included quality of life, exacerbations of the disease, hospitalisations and mortality. The study showed that, compared to placebo, tiotropium decreased lung function decline in patients not using inhaled corticosteroids or other long-acting bronchodilators, it significantly improved the mean value of FEV_1 and the quality of life (as evaluated with SGRQ). Treatment with tiotropium extended the time before the first exacerbation (median 16.7 months) compared to the patients who received placebo (median 12.5 months). The incidence of exacerbation was found to be lower in the tiotropium group than in the placebo group by 14% (0.73 vs 0.85 exacerbations/patient-year; hazard ratio (HR) 0.86) and the duration of exacerbations was shorter (12.1 vs 13.6 days/patient-year, HR 0.89). Moreover, treatment with tiotropium resulted in extending the time before an exacerbation leading to hospitalization (HR = 0.86). A still greater benefit for the endpoint regarding the effect on exacerbations has been shown by an analysis of the findings of the UPLIFT study in the subgroup of patients with moderate COPD (stage II according to the then valid GOLD standards). The number of exacerbations expressed in patient-years in the tiotropium group was lower by 20% than in the placebo group (HR 0.80; $p < 0.0001$). The time before an exacerbation or an exacerbation resulting in hospital admission was significantly longer in the tiotropium group than in the placebo group (HR 0.82 and 0.74; $p < 0.0001$ and $p = 0.001$, respectively) [19]. The findings of another analysis of the UPLIFT study conducted in the subgroup of patients with COPD who have not been treated earlier indicate that the slow-down of annual decrease in FEV_1 applies especially to patients in whom tiotropium was used as the first drug [20]. At least one exacerbation episode occurred in 55.6% of the patients in this subgroup treated with tiotropium and in 56.5% of patients who received placebo. There was a trend to lower incidence of exacerbations 16% in the tiotropium group compared to placebo, but the difference was not statistically significant (0.49 vs 0.58 exacerbations/year; $p = 0.08$). The time before the first exacerbation was not statistically different in the groups (26.9 in the tiotropium group vs 20.6 months in the placebo group, $p = 0.24$). Only 17% of patients suffered from an exacerbation that required hospitalisation, and the difference between the incidence of this type of exacerbations in both groups was not statistically significant.

The efficacy of tiotropium in the prevention of COPD exacerbations was evaluated in a meta-analysis of 9 randomised, placebo-controlled studies, with at least a 24-week follow-up period, covering a total of 6171 patients with COPD, including 2862 in the tiotropium group (18 μg) [21]. The findings of the analysis have confirmed the observations made in the UPLIFT study. A 21% reduction in the risk of exacerbations was achieved in the tiotropium group (HR 0.79; $p < 0.0001$). The risk of exacerbations was found to be smaller in 8 out of 9 studies (the effect size from 14% to 48%) and it was found to be the same in one — HR 1.03. Similarly, the risk of exacerbations that required hospitalisations was lower by 21% in the tiotropium group compared to the placebo group (HR 0.79; $p = 0.015$). In this case, the hazard ratio was smaller than 1 in 6 out of 9 studies. The treatment with tiotropium also resulted in extending the time until the first exacerbation. An exacerbation occurred up to week 46 in a much smaller percentage of patients treated with tiotropium (42.1% vs 50.8%). The treatment with tiotropium had a similar effect on the time until the first hospitalised exacerbation. A lower percentage of patients with hospitalised exacerbations was recorded in week 46 of the study in the tiotropium group compared to the control group (8.5% vs 10.8%). An additional analysis in subgroups confirmed that the beneficial effect of tiotropium on exacerbations did not depend on the age, gender, FEV_1 or the use of inhaled glucocorticosteroids.

An assessment of the efficacy of tiotropium was also the subject of a meta-analysis in the Cochrane library published in 2014, which assessed the results of 22 randomised, placebo-controlled clinical trials involving 23,309 COPD patients [22]. The follow-up period was between 3 months and 4 years. Nineteen out of 22 studies evaluated efficacy of tiotropium administered with a Handihaler inhaler; in the other 3 — tiotro-

pium was administered with a Respimat inhaler. An analysis of data from 22 studies showed that treatment with tiotropium significantly reduced the percentage of patients with exacerbations (38% vs 44%, odds ratio (OR) 0.78, 95% CI 0.70 to 0.87). This means that in order to avoid one exacerbation episode, 16 patients should be treated with tiotropium for one year (number needed to treat, NNT = 16; 95% CI, 10 to 36). The risk of exacerbations was not found to depend on the type of inhaler used to administer tiotropium, severity of the disease, duration of treatment or the use of inhaled glucocorticosteroids. Additionally, the effect of tiotropium on the incidence of hospitalised exacerbations was evaluated on the basis of 21 clinical trials. The percentage of patients who needed to be hospitalised because of exacerbations was lower in the tiotropium group than in the control group (10.4% vs 13.1%; OR 0.85, 95% CI 0.72 to 1.00).

Tiotropium vs Salmeterol

The GOLD guidelines regarding COPD treatment recommend the use of long-acting bronchodilators in order to alleviate the symptoms and reduce the risk of exacerbations in COPD patients at the moderate to severe stage, but it does not indicate whether long acting β_2-agonists (LABA) or long-acting cholinolitics (LAMA) are preferred [8]. A one-year randomised, double-blind POET-COPD (Prevention Of Exacerbations with Tiotropium in COPD) study compared the efficacy of tiotropium (LAMA) at the dose of 18 μg once daily with salmeterol (LABA) at 50 μg twice daily in a group of 7,376 patients with moderate to severe COPD (stage II-IV according to GOLD) [23]. It was shown in regards to the main endpoint that tiotropium treatment resulted in a longer (by 42 days) period until the first exacerbation than salmeterol (187 vs 145 days; time is defined as the number of days of treatment after which an exacerbation occurred; HR 0.83; $p < 0.001$). Compared to salmeterol treatment, the incidence of moderate and severe exacerbations in the group treated with tiotropium was smaller by 11% (0.64 vs 0.72 events/patient-year; relative risk (RR) 0.89; $p = 0.002$) and the incidence of severe exacerbations was smaller by 27% (0.09 vs 0.13 events/patient-year; RR 0.73, $p < 0.001$). Moreover, the incidence of exacerbations which require treatment with glucocorticosteroids administered systemically, the incidence of exacerbations treated with antibiotics and the incidence of exacerbations which require treatment with antibiotics and glucocorticosteroids administered systemically was lower in the tiotropium group compared to the salmeterol group, by 18% (0.33 vs 0.41 RR 0.82 and $p < 0.001$), 10% (0.53 vs 0.59 RR 0.90 and $p = 0.004$) and 20% (0.23 vs 0.28 RR 0.80 and $p < 0.001$), respectively. An analysis in subgroups showed that the beneficial effect of tiotropium on the period until the first exacerbation and on the incidence of exacerbations (number of events per patient-year) did not depend on the age, gender, severity of the disease, smoking, BMI (body-mass index) or the use of inhaled glucocorticosteroids.

Tiotropium vs ipratropium bromide

A comparison of efficacy of tiotropium with a short acting muscarinic antagonist (SAMA), ipratropium bromide, was the subject of a systematic review from the Cochrane library published in 2013 [24]. The analysis covered two randomised clinical trials with the follow-up period of at least 12 weeks, in which a total of 1,073 patients with stable chronic obstructive pulmonary disease took part. Tiotropium was administered from a HandiHaler inhaler in one study (at 18 μg), and from a Respimat inhaler (at 5 and 10 μg) in the other. The following were observed in the study as compared to ipratropium treatment: improvement in pulmonary function (FEV_1), better quality of life and a similar risk of death from any cause. In terms of exacerbations, both studies reported the number of patients with exacerbations, although an exacerbation episode was not defined clearly. A much smaller number of patients with at least one exacerbation was found in the tiotropium group compared to the ipratropium (OR 0.71). In one study, in which the incidence of exacerbations was also taken into account, it was shown that tiotropium treatment resulted in a 24% reduction in the incidence of exacerbations compared to ipratropium (0.73 vs 0.96; $p = 0.006$) [25]. Moreover, compared to ipratropium, tiotropium treatment considerably delayed the onset of an exacerbation, it extended the time until the first hospitalisation due to an exacerbation and shortened the period of exacerbations by 39% (10.8 vs 17.7 days/patient-year, $p = 0.002$). There was a trend to lower incidence of hospitalisations caused by exacerbations by 38% in the tiotropium group compared to the ipratropium group, but the difference was not statistically significant (0.10 vs 0.16; $p = 0.08$).

Tiotropium vs glycopyrronium

Apart from tiotropium, there is also another LAMA taken once daily – glycopyrronium. In a randomised, blinded phase II clinical trial called

GLOW5 (Glycopyrronium bromide in COPD airWays clinical trial study), the effect of glycopyrronium was compared to that of tiotropium in a group of 657 patients with moderate to severe COPD [26]. Glycopyrronium was administered at the dose 50 μg once daily, and tiotropium — at 18 μg, also once daily. The treatment period was 12 weeks. One of the secondary outcomes was an evaluation of the effect of glycopyrronium vs tiotropium on exacerbations. The number of patients with a moderate or severe exacerbation was low in both groups (9.7% and 7.5% in the glycopyrronium and tiotropium groups, respectively). Similarly, the incidence of exacerbations in the groups of glycopyrronium and tiotropium was low and comparable (0.38 exacerbations a year vs 0.35 exacerbations a year; RR 1.10; p = 0.754). The time until the first moderate or severe exacerbation of COPD did not differ significantly between the groups (HR 1.33; p = 0.324). No significant differences were observed between the glycopyrronium and the tiotropium groups in regards to the percentage of patients with exacerbations leading to hospitalizations (0.7% vs 1.0%, OR 0.79; p = 0.728), with exacerbations that require treatment with glucocorticosteroids administered systemically (6.0% vs 6.2%, OR 1.06; p = 0.728) and with exacerbations that require antibiotic treatment (8.3% vs 5.8%; OR 1.48; p = 0.236).

Tiotropium vs indacaterol

The effect of tiotropium and an ultra-long-acting β_2-agonist (ultraLABA), indacaterol, was compared in one analysis in subgroups conducted as part of the systematic review from the Cochrane library in 2013 [27]. An analysis in the indacaterol subgroup covered randomised clinical trials with the follow-up period of at least 12 weeks, with the total of 2,856 patients with moderate or severe COPD [28, 29]. It must be mentioned that the tiotropium arm was not blinded in one of the studies [28]. Another issue is that the design of the analysed studies is different, number of patients varies between arms, and the definition of exacerbations may be slightly different in presented trials. No other exacerbation indexes were reported in either of the studies.

Summary

Results of the clinical trials have confirmed a beneficial effect of tiotropium on exacerbations. Compared to placebo, tiotropium reduces the incidence of exacerbation episodes, reduces the duration of exacerbations and delays onset of events, which also includes exacerbations leading to hospitalizations. The beneficial effect of tiotropium on exacerbations is particularly clear in patients with moderate COPD (stage II according to GOLD). Tiotropium is more effective than salmeterol and ipratropium in terms of reduction in exacerbation incidence. The effect of tiotropium on exacerbations cannot be compared to that of glycopyrronium and indacaterol because of limited clinical data and absence of statistically significant differences between the treatment regimens under study.

Conflict of interest

Paweł Szepiel is an employee of the Boehringer Ingelheim.

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